

# Retigabine (ezogabine) as add-on therapy for partial-onset seizures: an update for clinicians

Jacklyn A. Harris and Julie A. Murphy

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## Abstract:

**Objective:** The present study reviewed the pharmacology, pharmacokinetics, efficacy, and safety of retigabine (ezogabine), a potential agent for use as adjunctive treatment in refractory partial-onset seizures.

**Methods:** A MEDLINE search (1966–May 2011) was conducted using the key words retigabine, ezogabine, D-23129, epilepsy, and anticonvulsant. Bibliographies of all articles retrieved were also reviewed. All studies including humans and published in English with data describing retigabine for the adjunctive treatment of partial-onset seizures were reviewed.

**Results:** Retigabine has been shown to interact with the KCNQ2/KCNQ3 subunits of the potassium channels, GABA<sub>A</sub> receptors, and weakly block sodium and calcium channels. Retigabine is 50–60% bioavailable, metabolized by N-glucuronidation and N-acetylation, 80% protein bound, and has few drug–drug interactions. Recent data suggest that retigabine may have a role as adjunctive treatment for refractory partial-onset seizures. Placebo-controlled trials demonstrated a 23.4–44.3% reduction in seizure frequency with 50% responder rates ranging from 23.2% to 47.0% with varying doses of retigabine. The most common adverse effects, occurring in greater than 10% of subjects in the clinical trials, include abnormal gait, confusion, dizziness, fatigue, headache, nausea, somnolence, speech disorder, tremor, urinary tract infection, and blurred vision.

**Conclusions:** Retigabine is a promising agent for adjunctive treatment of refractory partial-onset seizures.

**Keywords:** epilepsy, ezogabine, partial-onset seizures, retigabine

## Introduction

The annual incidence of epilepsy is approximately 40–70 per 100,000 individuals [De Boer *et al.* 2008]. Over 60% of all patients diagnosed with epilepsy experience partial-onset seizures [Schmitz *et al.* 2010]. Despite optimal use of first- and/or second-generation anti-epileptic drugs (AEDs), approximately 30% of patients will have refractory seizures [Luszczki, 2009; De Boer *et al.* 2008]. This has led to the development of novel AEDs, making up the third-generation class. The AEDs in the third-generation class have a wide array of mechanisms involving the voltage-gated sodium channels, N-methyl-D-aspartate receptors, chloride channels, GABA<sub>A</sub> receptors, collapsing response mediator protein-2, and the  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors [Luszczki, 2009]. Retigabine

(international nonproprietary name, codename D-23129, US adopted name [USAN] ezogabine) has been shown to be the one novel AED that works by activating potassium channels. Researchers suspect that retigabine will benefit those patients with refractory partial-onset seizures due to its unique mode of action. This review explores the role of retigabine as an adjunct to the management of partial-onset seizures.

## Methods

### Data sources

A literature review was conducted consisting of a MEDLINE database search of articles using the search terms retigabine, ezogabine, D-23129, epilepsy, and anticonvulsant. The search was limited to those articles involving humans and

Correspondence to:  
**Jacklyn A. Harris,  
PharmD, BCPS**

Assistant Professor of  
Pharmacy Practice,  
Department of Pharmacy  
Practice, St Louis College  
of Pharmacy, 4588  
Parkview Place, St Louis,  
MO 63110-1088, USA  
**jharris2@stlcop.edu**

**Julie A. Murphy, PharmD,  
BCPS**  
Associate Professor of  
Pharmacy Practice, St  
Louis College of  
Pharmacy, St Louis, MO,  
USA

written in English. A total of 47 articles describing retigabine for the adjunctive treatment of refractory partial-onset seizures were identified with this search. In this review 27 articles were excluded because they only referenced animal studies ( $n=8$ ), or were review articles that discussed the proposed correlation between potassium channels and epilepsy with little information about retigabine ( $n=7$ ), or included limited discussion about retigabine ( $n=12$ ). The bibliographies of the included articles were then reviewed for other relevant articles not included in the MEDLINE search. Eight additional articles were identified.

## Results

### Pharmacology

Retigabine (N-[2-amino-4-(fluoro-benzylamino)-phenyl]-carbamic acid ethyl ester) has been shown to interact with potassium channels, GABA<sub>A</sub> receptors, and weakly block sodium and calcium channels [Luszczki, 2009]. The mechanism unique to retigabine is its ability to activate potassium channels, specifically KCNQ2/KCNQ3 subunits, decreasing the excitability of neurons [Luszczki, 2009; Armijo *et al.* 2005]. The KCNQ2/KCNQ3 genes found in the hippocampus, neocortex, and thalamus contribute to the M-current, which is inhibited by the activation of muscarinic acetylcholine receptors [Armijo *et al.* 2005]. The M-current activates slowly following depolarization, and does not inactivate with sustained depolarization. When reducing M-current activity, neuronal excitability is enhanced predisposing to seizures. In contrast, activating the M-current suppresses bursting and epileptiform activity while allowing responses to ordinary excitatory inputs. This activity causes researchers to suspect that enhancing M-current activity could potentially protect against seizure activity [Rogawski and Bazil, 2008]. The association between benign familial neonatal convulsions (BFNC) and KCNQ2/KCNQ3 genes has further validated the researchers' hypothesis [Cooper, 2001]. Further research using the *Xenopus* oocyte system found large voltage-dependent potassium channels as a result of *in vitro* injections of both KCNQ2 and KCNQ3 RNA. A reduction, up to 95%, in the size of the potassium channel currents was seen in the mutations associated with BFNC. Epilepsy may then be the result of modest reductions in the amount of KCNQ channel activity [Schroeder *et al.* 1998].

Retigabine also potentiates GABA<sub>A</sub> receptor responses at higher concentrations than are effective on potassium channels [Luszczki, 2009; Rogawski and Bazil, 2008; Porter *et al.* 2007a; Rogawski, 2006]. The activity against GABA receptors, however, was found to be ineffective against the administration of flumazenil, indicating that retigabine differs mechanistically from benzodiazepines [Rogawski and Bazil, 2008; Porter *et al.* 2007a; Rogawski, 2006].

### Pharmacokinetics

Retigabine's rapid absorption is unaffected by food with an absolute bioavailability of 50–60%. It achieves peak plasma concentration within 1.5 h after administration. Retigabine has a half-life of 8–11 h, and is about 80% plasma protein bound [Nasreddine *et al.* 2010; Landmark and Johannessen, 2008; Ferron *et al.* 2002]. It is metabolized by N-glucuronidation and N-acetylation resulting in two inactive metabolites [Bialer *et al.* 2010; Luszczki, 2009; Landmark and Johannessen, 2008; Hermann *et al.* 2003a]. Both active retigabine and its metabolites are exclusively eliminated renally [Bialer *et al.* 2010; Luszczki, 2009; Landmark and Johannessen, 2008]. Clearance of retigabine in the elderly is 30% lower when compared with younger subjects; however, researchers suspect this difference is most likely due to age-related renal function changes [Hermann *et al.* 2003a].

Since retigabine is not metabolized by the cytochrome P450 system, minimal pharmacokinetic drug interactions have been found [Nasreddine *et al.* 2010; Luszczki, 2009; Landmark and Johannessen, 2008]. A study evaluating the potential interaction between retigabine and phenobarbital revealed no pharmacokinetic interaction between the two AEDs [Ferron *et al.* 2003]. However, co-administration of retigabine with lamotrigine resulted in a small decrease in retigabine clearance, which is thought to be due to competition for renal elimination. Retigabine was also found to increase the metabolism of lamotrigine by an unknown mechanism [Hermann *et al.* 2003b]. The pharmacokinetics of valproic acid, topiramate, phenytoin, or carbamazepine was not clinically altered with concurrent retigabine use. Oral combination contraceptives and retigabine do not result in any pharmacokinetic interactions [Bialer *et al.* 2010; Luszczki, 2009; Hermann *et al.* 2003b].

### Clinical trials

In a parallel-group, double-blind, placebo-controlled, randomized clinical trial, the 16-week (8-week forced titration and 8-week maintenance) efficacy and safety of adjunctive therapy with retigabine 600 mg, 900 mg, and 1200 mg/day in three equally divided doses in subjects with partial-onset seizures was evaluated [Porter *et al.* 2007b]. During the 8-week baseline phase, subjects had to experience a minimum of four partial-onset seizures per month with no 30-day seizure-free period, while maintained on stable doses of one or two AEDs. During week one of the forced titration phase, subjects in the retigabine arms received retigabine 100 mg three times daily. At weekly intervals, thereafter, the dose was increased by 150 mg/day (50 mg three times daily), such that subjects in the 600 mg/day arm reached their target dose by day 15, the 900 mg/day arm by day 29, and the 1200 mg/day arm by day 43. A total of 396 subjects were included in the intention-to-treat (ITT) efficacy analysis. The median percentage reduction in monthly total partial seizure frequency from baseline and the 50% responder rates can be found in Table 1. Adverse events that occurred are addressed in the adverse drug reactions section below. The authors concluded that adjunctive therapy with retigabine is well tolerated and reduces the frequency of partial-onset seizures in a dose-dependent manner.

The Retigabine Efficacy and Safety Trials for Partial Onset Epilepsy Study 302 (RESTORE 2) was a randomized, double-blind, placebo-controlled, multicenter, parallel-group study that evaluated the efficacy and safety of adjunctive retigabine 600 mg and 900 mg/day,

administered at 8-h intervals, in subjects with refractory partial-onset seizures [Brodie *et al.* 2010]. The study consisted of four phases: a prospective 8-week baseline, 4-week titration, 12-week maintenance, and a 4-week transition phase for subjects electing to participate in an open-label extension. During the 8-week prospective baseline phase, subjects had to experience a minimum of four partial-onset seizures per 28 days without a seizure-free period of more than 21 days while maintained on stable doses of one to three AEDs. During the titration phase, the starting dose of 300 mg/day (100 mg every 8 h) was increased by 150 mg/day (50 mg every 8 h) at 1-week intervals, reaching the target dose by the end of week two (600 mg/day [200 mg every 8 h]) or week four (900 mg/day [300 mg every 8 h]) of treatment. The ITT Food and Drug Administration (FDA) population ( $n=538$ ) was defined as all randomized subjects receiving at least one dose of study drug; this was also the safety population. The European Medicines Agency (EMEA) population ( $n=471$ ) was defined as all randomized subjects who received at least one dose of study drug and had at least one seizure measurement recorded in the maintenance phase. The median percentage reduction in 28-day total partial-seizure frequency from baseline and the 50% responder rates can be found in Table 1. Adverse events that occurred are addressed in the adverse drug reactions section below. The authors concluded that adjunctive therapy with retigabine was effective and generally well tolerated in adults with refractory partial-onset seizures.

The Retigabine Efficacy and Safety Trials for Partial Onset Epilepsy Study 301 (RESTORE 1)

**Table 1.** Summary of placebo-controlled trials for retigabine in partial-onset seizures.

Study	Sample size	Dosage	Median reduction in seizure frequency	50% responder rates
Porter <i>et al.</i> [2007b]	$n=396$	Placebo 600 mg/day 900 mg/day 1200 mg/day	13.1% 23.4% ( $p < 0.001$ ) 29.3% ( $p < 0.001$ ) 35.2% ( $p < 0.001$ )	15.6% 23.2% 31.6% ( $p = 0.0214$ ) 33.0% ( $p = 0.0214$ )
Brodie <i>et al.</i> [2010] (RESTORE 2)	Food and Drug Administration population ( $n=538$ ) European Medicines Agency population ( $n=471$ )	Placebo 600 mg/day 900 mg/day Placebo 600 mg/day 900 mg/day	15.9% 27.9% ( $p = 0.007$ ) 39.9% ( $p < 0.001$ ) 5.1% 25.0% ( $p = 0.002$ ) 30.9% ( $p < 0.001$ )	17.3% 31.5% ( $p = 0.002$ ) 39.3% ( $p < 0.001$ ) 18.9% 38.6% ( $p < 0.001$ ) 47.0% ( $p < 0.001$ )
French <i>et al.</i> [2011] (RESTORE 1)	$n=305$	Placebo 1200 mg/day	17.5% 44.3% ( $p < 0.001$ )	17.8% 44.4% ( $p < 0.001$ )

RESTORE, Retigabine Efficacy and Safety Trials for Partial Onset Epilepsy.

was a multinational, multicenter, randomized, double-blind, parallel-group, placebo-controlled trial that evaluated the efficacy and safety of adjunctive retigabine 1200 mg/day, administered at 8-h intervals, in subjects with refractory partial-onset seizures [French *et al.* 2011]. The study consisted of three phases: a prospective 8-week baseline, 6-week dose titration, and a 12-week maintenance phase. During the 8-week prospective baseline phase, subjects had to experience a minimum of four partial-onset seizures per 28 days while receiving stable doses of one to three AEDs. During the titration phase, the starting dose of 300 mg/day (100 mg every 8 h) was increased by 150 mg/day (50 mg every 8 h) at 1-week intervals, reaching the target dose of 1200 mg/day at week six. A total of 305 subjects were included in the ITT efficacy analysis. The median percentage reduction in 28-day total partial-seizure frequency from baseline and the 50% responder rates for the 18-week treatment period can be found in Table 1. Adverse events that occurred are addressed in the adverse drug reactions section below. The authors concluded that retigabine is effective as adjunctive therapy for reducing seizure frequency in patients with refractory partial-onset seizures.

#### *Adverse drug reactions*

The adverse effects that occurred in at least 5% of subjects in at least one of the clinical trials discussed are summarized in Table 2.

In the RESTORE 2 trial, chromaturia was reported in one and two subjects in the 600 mg/day and 900 mg/day groups, respectively, *versus* one subject in the placebo group [Brodie *et al.* 2010]. One subject withdrew from the trial due to nephritis and two due to urinary retention. In the RESTORE 1 trial, urinary retention was reported by two placebo-treated subjects and one retigabine-treated subject [French *et al.* 2011]. The authors reported that urinary tract infection, urinary hesitation, dysuria, and chromaturia occurred in more subjects receiving retigabine than placebo, but that these effects were not serious, and improved or resolved spontaneously or upon treatment discontinuation. There were no clinically relevant findings related to urinary bladder function in the trial carried out by Porter and colleagues [Porter *et al.* 2007b].

Porter and colleagues reported that subjects receiving 1200 mg/day of retigabine experienced a 2–3% increase in body weight and those in the

**Table 2.** Adverse effects associated with retigabine [Porter *et al.* 2007b; Brodie *et al.* 2010; French *et al.* 2011].

Adverse effects	Subjects in trials (%)
Abnormal gait	5.6–11.8
Amnesia	5.6
Anxiety	5.2
Asthenia	5.8
Confusion	12.3–14.4
Constipation	5.9
Diplopia	6.1–6.5
Disturbance in attention	5.2–6.4
Dizziness	14.6–40.5
Dysuria	5.2
Fatigue	15.7–16.2
Headache	12.4–14.2
Influenza	7.8
Memory impairment	5.0–7.8
Nausea	6.4–10.5
Somnolence	20.3–31.4
Speech disorder	8.5–12.4
Thinking abnormal	9.0
Tremor	5.3–11.1
Urinary hesitation	5.9
Urinary tract infection	11.8
Vertigo	5.9–9.3
Vision blurred	11.8
Vomiting	5.2

900 mg/day arm experienced a 1% increase in body weight [Porter *et al.* 2007b]. In the RESTORE 2 trial, minor increases in weight, 1.1 kg and 1.4 kg in the 600 mg/day and 900 mg/day groups, respectively, were seen at week 16 *versus* an average decrease in weight of 0.1 kg in the placebo group [Brodie *et al.* 2010]. In the RESTORE 1 trial, subjects receiving retigabine experienced a 3.5% increase in body weight *versus* a 0.4% increase in the placebo group [French *et al.* 2011].

In the RESTORE 2 trial, an increase in liver enzymes (greater than three times the upper limit of normal) that normalized spontaneously was seen in seven, three, and six subjects in the placebo, 600 mg/day, and 900 mg/day groups, respectively [Brodie *et al.* 2010]. In the RESTORE 1 trial, rare transient abnormal liver function tests were observed [French *et al.* 2011].

There were no clinically relevant findings related to retigabine treatment on vital signs, laboratory measurements (besides the liver enzymes discussed above), electrocardiogram findings (particularly QTc interval), neurologic examinations, or ophthalmologic examinations in the clinical

trials discussed [French *et al.* 2011; Brodie *et al.* 2010; Porter *et al.* 2007b].

#### *Contraindications and precautions*

The clinical trials discussed in this review do not specify any contraindications or precautions for the use of retigabine. The report from the tenth Eilat conference (EILAT X) indicates concern for dose-related bladder dysfunction including dysuria and urinary hesitation [Bialer *et al.* 2010]. In August 2010, the FDA's Peripheral and Central Nervous System Drugs Advisory Committee expressed concern over the potential for urinary retention with retigabine [Lowry, 2010]. While the advisory committee believes the urinary retention may be minimized with patient monitoring, it is not known what this monitoring should entail.

#### *Dosage and administration*

In the clinical trials discussed in this review, retigabine was administered orally at a dose of 600–1200 mg/day in three evenly divided doses [French *et al.* 2011; Brodie *et al.* 2010; Porter *et al.* 2007b]. The initial dosage was 300 mg/day (100 mg administered three times daily), which was increased by 150 mg/day (50 mg three times daily) to the target dose. Doses were administered approximately 8 h apart.

#### **Conclusion**

Retigabine (Trobalt®) was approved by the EMEA on 28 March 2011 as adjunctive treatment of partial-onset seizures with or without secondary generalization in adults aged 18 years and above with epilepsy. On 10 June 2011, the FDA approved retigabine (USAN, ezogabine, Potiga®) for the adjunctive treatment of partial-onset seizures in patients aged 18 years and older [FDA, 2011]. Based on the evidence of retigabine's effectiveness for the adjunctive treatment of partial-onset seizures in the clinical trials described here, it appears that the drug consistently reduces seizure frequency for this patient population. This, in addition to the drug's novel mechanism of activating the KCNQ2/KCNQ3 subunits of the potassium channels and a fairly benign side-effect profile, makes retigabine an attractive alternative to other approved AEDs for the adjunctive treatment for partial-onset seizures. Retigabine is also being investigated to determine its role in the treatment of neuropathic pain, bipolar disorder, migraine headaches, and restless legs syndrome.

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#### **Conflict of interest statement**

The authors declare no conflicts of interest in preparing this article.

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